

CLAIMS

1. A method for protecting the stratified squamous epithelium of an individual against injury by a noxious substance comprising:  
administering to the epithelium an effective amount of an agent comprising:  
a) at least one aromatic group;  
b) at least one  $-\text{OSO}_3\text{R}^4$  moiety, wherein  $\text{R}^4$  is H or a pharmaceutically acceptable cation; and  
c) at least one -NCS, -NCO, -NH(CO)-OR<sup>3</sup>, -NH(CS)SR<sup>3</sup>, -NH(C=NH)OR<sup>3</sup>, -NHCOCH<sub>2</sub>Cl, -NHCOCH<sub>2</sub>Br, -NHCO-CH=CH<sub>2</sub>, or -NHC(O)-CF<sub>3</sub> moiety.
2. The method of claim 1, wherein the at least one  $-\text{OSO}_3\text{R}^4$  moiety is non-annular to the aromatic group.
3. The method of claim 1, wherein the at least one aromatic group(s) is selected from the group consisting of phenyl, pyridyl, naphthyl, quinolyl and isoquinolyl.
4. The method of claim 3, wherein the at least one aromatic group(s) is phenyl.
5. The method of claim 1, wherein the agent comprises at least two aromatic groups.
6. The method of claim 1, wherein the agent further comprises a C<sub>3</sub>-C<sub>8</sub> cycloalkyl.
7. The method according to claim 1, wherein the agent comprises at least one -NCS moiety.
8. The method according to claim 1, wherein said noxious substance is selected from the group consisting of gastric acid, HCl, N-acetylcysteine, acid-pepsin, and pepsin.
9. The method according to claim 1, wherein the individual is mammal.

10. The method according to claim 9, wherein said agent is administered at a dosage of about 0.1-50 mg.

11. The method according to claim 9, wherein said agent is administered at a concentration of about 40 nM to about 4  $\mu$ M.

12. The method according to claim 9, wherein the mammal is a human.

13. The method according to claim 9, wherein said mammal suffers from gastroesophageal reflux disease (GERD), heartburn, laryngitis, or pharyngitis.

14. The method according to claim 13, wherein said mammal suffers from gastroesophageal reflux disease (GERD).

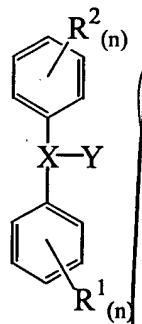
15. The method according to claim 1, wherein the epithelium is selected from the group consisting of buccal, oropharyngeal, esophageal and laryngeal epithelium, rumen and forestomach.

16. The method according to claim 15, wherein the epithelium is esophageal epithelium.

17. The method according to claim 1, wherein said agent is administered by: perfusion via a tube onto the surface of stratified squamous epithelium; oral ingestion; gum; lozenge; mouth rinse; or aerosol spray.

18. A method for protecting stratified squamous epithelium against injury by a noxious substance comprising:

administering to the epithelium an effective amount of an agent of the formula:



wherein X is a linker selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>2</sub>-C<sub>6</sub> alkenylene, or C<sub>3</sub>-C<sub>6</sub> alkynylene, wherein X may optionally include 1 or 2 oxygen atoms and/or 1 sulfur atom;

Y is a group pendant from X comprising at least one -OSO<sub>3</sub>R<sup>4</sup> moiety, wherein R<sup>4</sup> is H or a pharmaceutically acceptable cation;

n is an integer from 1-3; and

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of -H, a halogen with an atomic number from 9 to 53, hydroxy, -SO<sub>3</sub>R<sup>4</sup>, -OSO<sub>3</sub>R<sup>4</sup>, -NCS, -NCO, -NH(CO)-OR<sup>3</sup>, -NH(CS)SR<sup>3</sup>, -NH(C=NH)OR<sup>3</sup>, -NHCOC<sub>2</sub>Cl, -NHCOC<sub>2</sub>Br, -NHCOC-CH=CH<sub>2</sub>, -NHC(O)-CF<sub>3</sub>, -S-CH<sub>2</sub>-CH=CH<sub>2</sub>, -NHCH<sub>2</sub>-C≡CH, -NH-CH<sub>2</sub>-CN, -NH-S-CH<sub>2</sub>-CH=CH<sub>2</sub>, -O-CH<sub>2</sub>-CH=CH<sub>2</sub>, -NH-CF<sub>3</sub>, N-mono-, di-, tri-, tetra- and penta-haloethyl, -CN, -NH<sub>2</sub>, -NO<sub>2</sub>, -NHCOC<sub>3</sub>H<sub>7</sub>, -CHO, -COOR<sup>4</sup>, -N<sub>3</sub>, -COR<sup>3</sup>, -R<sup>3</sup>OH, -R<sup>3</sup>NHCOC<sub>3</sub>H<sub>7</sub>, -R<sup>3</sup>OSO<sub>3</sub>R<sup>4</sup>, -R<sup>3</sup>SO<sub>3</sub>R<sup>4</sup>, -OR<sup>3</sup>, -SR<sup>3</sup> and -R<sup>3</sup>, wherein R<sup>3</sup> is p-nitrophenyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, or C<sub>2</sub>-C<sub>6</sub> alkynyl, if at the distal end of the substituent, or C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>2</sub>-C<sub>6</sub> alkenylene, or C<sub>2</sub>-C<sub>6</sub> alkynylene, if at the proximal end of the substituent, and wherein R<sup>4</sup> is H or a pharmaceutically acceptable cation.

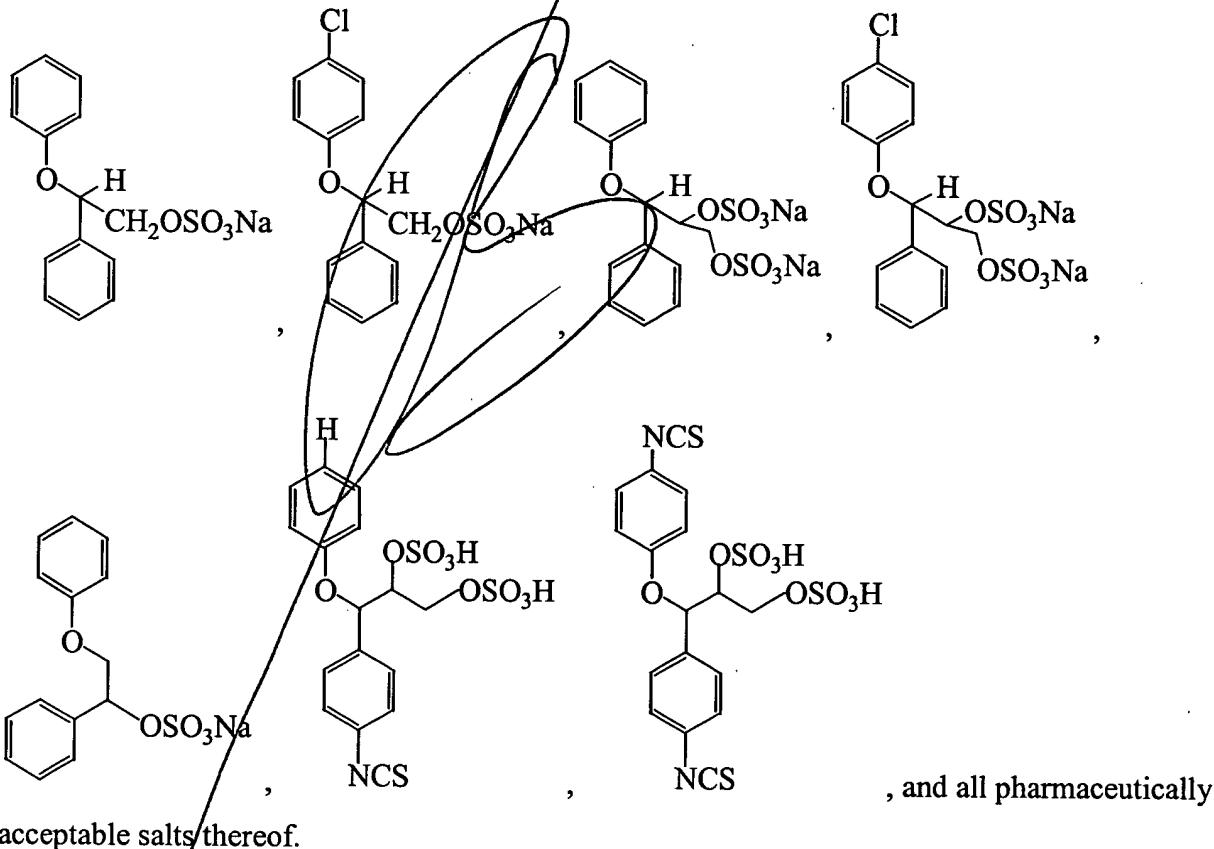
19. The method of claim 18, wherein at least one of R<sub>1</sub> and R<sub>2</sub> is -NCS.
20. The method of claim 18, wherein X is -OCH<sub>2</sub>- or -CH<sub>2</sub>O-.
21. The method of claim 18, wherein Y is C<sub>1</sub> to C<sub>4</sub> alkyl, to which is attached at least one -OSO<sub>3</sub>R<sup>4</sup> moiety.

22. The method of claim 18, wherein Y is a sulfonated polycarbinol chain of 1 to 6 sulfonated carbon atoms.

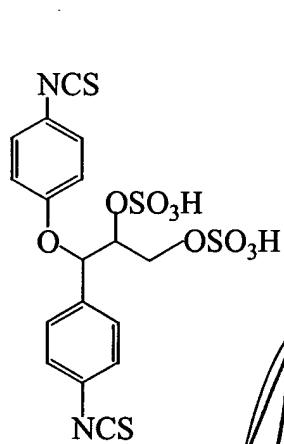
23. The method of claim 18, wherein Y comprises at least two -OSO<sub>3</sub>R<sup>4</sup> moieties.

24. The method of claim 18, wherein Y is ethyl-1,2-disulfate.

25. The method of claim 18, wherein the agent is selected from the group consisting of:

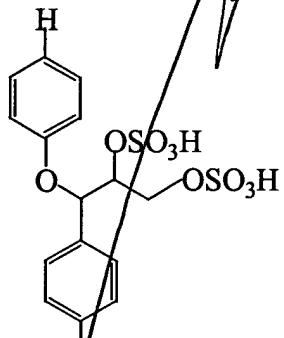


26. The method of claim 25, wherein the agent is



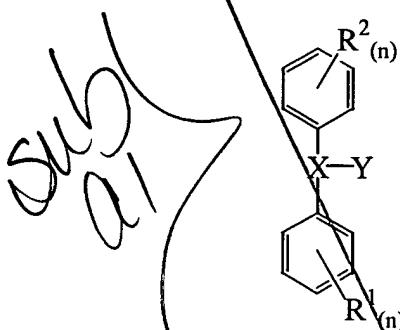
, or a pharmaceutically acceptable salt thereof.

27. The method of claim 25, wherein the agent is



, or a pharmaceutically acceptable salt thereof.

28. An agent which protects stratified squamous epithelium against injury by a noxious substance, and has the formula:



wherein: X is a linker selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>2</sub>-C<sub>6</sub> alkenylene, or C<sub>3</sub>-C<sub>6</sub> alkynylene, wherein X may optionally include 1 or 2 oxygen atoms and/or 1 sulfur atom;

*Sub 3*  
Y is a group pendant from X comprising at least one  $-\text{OSO}_3\text{R}^4$  moiety, wherein  $\text{R}^4$  is H or a pharmaceutically acceptable cation;

n is an integer from 1-3; and

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of -H, a halogen with an atomic number from 9 to 53, hydroxy,  $-\text{SO}_3\text{R}^4$ ,  $-\text{OSO}_3\text{R}^4$ , -NCS, -NCO, -NH(CO)-OR<sup>3</sup>, -NH(CS)SR<sup>3</sup>, -NH(C=NH)OR<sup>3</sup>, -NHCOCH<sub>2</sub>Cl, -NHCOCH<sub>2</sub>Br, -NHCO-CH=CH<sub>2</sub>, -NHC(O)-CF<sub>3</sub>, -S-CH<sub>2</sub>-CH=CH<sub>2</sub>, -NHCH<sub>2</sub>-C≡CH, -NH-CH<sub>2</sub>-CN, -NH-S-CH<sub>2</sub>-CH=CH<sub>2</sub>, -O-CH<sub>2</sub>-CH=CH<sub>2</sub>, -NH-CF<sub>3</sub>, N-mono-, di-, tri-, tetra- and penta-haloethyl, -CN, -NH<sub>2</sub>, -NO<sub>2</sub>, -NHCOCH<sub>3</sub>, -CHO, -COOR<sup>4</sup>, -N<sub>3</sub>, -COR<sup>3</sup>, -R<sup>3</sup>OH, -R<sup>3</sup>NHCOCH<sub>3</sub>, -R<sup>3</sup>OSO<sub>3</sub>R<sup>4</sup>, -R<sup>3</sup>SO<sub>3</sub>R<sup>4</sup>, -OR<sup>3</sup>, -SR<sup>3</sup> and -R<sup>3</sup>, wherein R<sup>3</sup> is p-nitrophenyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, or C<sub>2</sub>-C<sub>6</sub> alkynyl, if at the distal end of the substituent, or C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>2</sub>-C<sub>6</sub> alkenylene, or C<sub>2</sub>-C<sub>6</sub> alkynylene, if at the proximal end of the substituent, and wherein R<sup>4</sup> is H or a pharmaceutically acceptable cation.

29. The agent of claim 28, wherein at least one of R<sub>1</sub> and R<sub>2</sub> is -NCS.

30. The agent of claim 28, wherein X is -OCH<sub>2</sub>- or -CH<sub>2</sub>O-.

31. The agent of claim 28, wherein Y is C<sub>1</sub> to C<sub>4</sub> alkyl, to which is attached at least one  $-\text{OSO}_3\text{R}^4$  moiety.

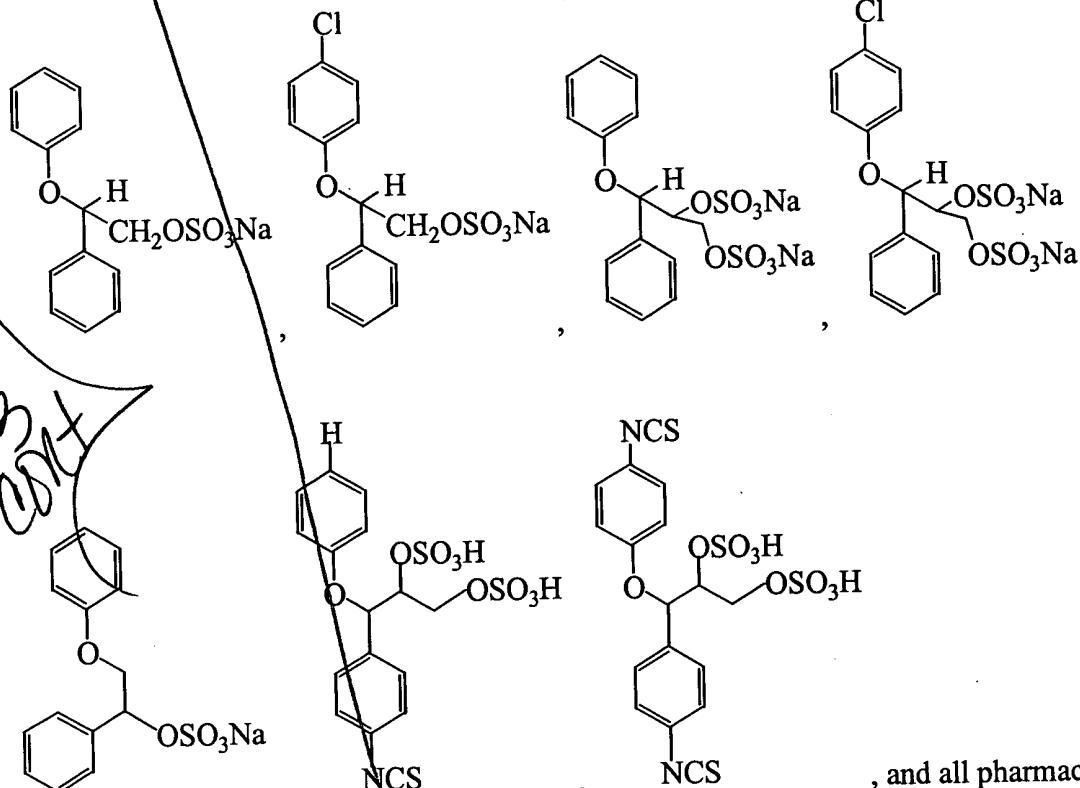
32. The agent of claim 28, wherein Y is a sulfonated polycarbinol chain of 1 to 6 sulfonated carbon atoms.

33. The agent of claim 28, wherein Y comprises at least two  $-\text{OSO}_3\text{R}^4$  moieties.

34. The agent of claim 28, wherein Y is ethyl-1,2-disulfate.

35. The agent of claim 28, wherein the agent is selected from the group consisting of:

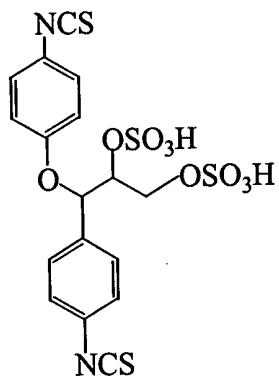
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, and all pharmaceutically

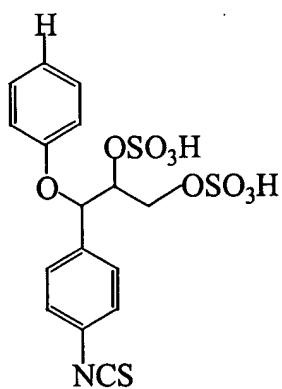
→ acceptable salts thereof.

36. The agent of claim 35, wherein the agent is



, or a pharmaceutically acceptable salt thereof.

37. The agent of claim 35, wherein the agent is



, or a pharmaceutically acceptable salt thereof.

38. A composition comprising an agent according to claim 28 and a pharmaceutically acceptable excipient.

39. A composition comprising an agent according to claim 28 and a proton pump inhibitor.

40. A kit for treating an individual who suffers from or is susceptible to gastroesophageal reflux disease (GERD), heartburn, laryngitis, or pharyngitis comprising:

- a container comprising an effective amount of an agent according to claim 28;
- instructions for use.

and

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